REMARKS

By this paper claims 1, 4, 5, 10, 12, 14-16, 18, 24-25, 29, and 33-34 are amended, claims 2-3, 6-9, 11, 17, 19-23, 26-28, 30-32, 35-40 are canceled, and new claims 41-44 are added. Therefore, after entry of this paper, claims 1, 4-5, 10, 12-16, 18, 24-25, 29, 33-34, and 41-44 will be pending. Support for the amendments to the claims, and for the new claims, can be found throughout the application and claims as filed.

I. Claim Rejections Under 35 U.S.C. §112, 1st Paragraph, Enablement

Claims 1-18 and 24-40 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Applicant respectfully disagrees with this rejection.

The Office Action asserts that the specification "while being enabling for a method of determining sprint, strength, or power performance in human males comprising: obtaining a sample from a human male, [and] analyzing the sample for the presence of the human ACTN3 577RR genotype, wherein the presence of the homozygous ACTN3 577RR genotype indicates an improved sprint, strength or power performance in a human male, does not reasonably provide enablement for predicting sprint performance, endurance performance, power performance in "any" male or "any" female in any mammalian species by the detection [of] any variation in the ACTN3 gene or [the] presence of [the] ACTN3 577RX or 577XX genotype."

The amendments to the claims presented herein render much of the Office Action's rejection moot. More specifically, the claims as presented herein are directed to humans as opposed to any mammal, and are directed to variations in the ACTN3 gene at the locus that encodes amino acid 577 as opposed to any variation in the ACTN3 gene, and are directed to methods of predicting potential sprint, strength, or power performance but not endurance performance.

With regard to the remainder of the rejection under 35 U.S.C. §112, first paragraph, the Office Action appears to suggest that specification is only enabling "for a method of determining sprint, strength, or power performance in human males comprising: obtaining a sample from a human male, [and] analyzing the sample for the presence of the human ACTN3 577RR genotype" (emphasis added), and is not enabling for the ACTN3 577RX or 577XX genotypes in

males or for any of the ACTN3 genotypes in females. Applicant respectfully disagrees with this rejection for the reasons enumerated below.

(i) Enablement of the Claimed Methods in Human Males

Applicant avers that the present application is enabling for a method of determining potential sprint, strength, or power performance in human males, comprising analyzing a sample for the presence of at least one 577R allele or for the presence of the 577XX genotype.

The data in the present application as filed demonstrates that the presence of at least one 577R allele is positively associated with sprint, power, and strength performance in males. The Examiner's attention is directed to Table 1 of the present application, which shows that in males the frequency of the R allele is 57% in control subjects and 72% in sprint/power athletes.

The data in the present application as filed demonstrates that the presence of the 577XX genotype allele is negatively associated with sprint, power, & strength performance in males. The Examiner's attention is directed to Table 1 of the present application, which shows that in males the frequency of the ACTN3 577XX genotype is 16% in control subjects and 8% in sprint/power athletes. New claims 41, as presented herein, is directed to a method of predicting athletic performance in a human comprising wherein the presence of the 577XX genotype is negatively associated with sprint, power, and strength performance.

(ii) Enablement of the Claimed Methods in Human Females

Applicant avers that the present application is enabling for a method of determining potential sprint, strength, or power performance in human females, comprising analyzing a sample for the presence of the at least one 577R allele or for the presence of the 577XX genotype.

The data in the present application as filed demonstrates that the presence of at least one copy of the 577R allele is positively associated with sprint, power, and strength performance in females. The Examiner's attention is directed to Table 1 of the present application, which shows that in females the frequency of the 577R allele is 55% in control subjects and 71% in sprint/power athletes.

The data in the present application as filed also demonstrates that the presence of the 577XX genotype allele is negatively associated with sprint, power, and strength performance in females. The Examiner's attention is directed to Table 1 of the present application, which shows that in females the frequency of the ACTN3 577XX genotype is 20% in control subjects and 0% in sprint/power athletes. New claims 41-43, as presented herein, encompass a method of predicting athletic performance in a human female wherein the presence of the 577XX genotype allele is negatively associated with sprint, power, and strength performance.

(iii) Burden on the Examiner Under the Enablement Requirement

The MPEP provides that:

> *"[i]n order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.....*
> *A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph,* ***unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.*** *" MPEP §2164.04 (emphasis added)*

In asserting that the present application is only enabling "for a method of determining sprint, strength, or power performance in human males comprising: obtaining a sample from a human male, [and] analyzing the sample for the presence of the human ACTN3 577RR genotype, the Office Action, suggests that the present application is not enabling for a method of determining sprint, strength, or power performance in human males comprising analyzing a sample for the presence of at least one R allele of for the presence of the 577XX genotype, or for a method of determining sprint, strength, or power performance in human females comprising determining analyzing a sample for the presence of any ACTN3 577 genotype.

As described in sections (i) and (ii) above, Applicant avers that the present application is enabling for such methods and provides data from experiments to support such methods.

The Office Action appears to place no weight on the data presented in the present application, even though that data was published in *The American Journal of Human Genetics* in 2003 (*See*, Yang, MacArthur, Gulbin, Hahn, Beggs, Eastel, and North. *Am. J. Hum. Genet.* 73: 627-631, July 23, 2003 (Table 1 in the present application, containing the data discussed herein, is identical to Table 1 in Applicant's 2003 *American Journal of Human Genetics* paper). The editor of the *American Journal of Human Genetics*, and the scientists who performed the peer review of the paper before it was accepted and published, clearly found Applicant data to be persuasive, and to support the conclusion, as stated in the abstract of published paper, that the authors' work "*demonstrate[s] highly significant associations between ACTN3 genotype and athletic performance. Both male and female elite sprint athletes have significantly higher frequencies of the 577R allele than do controls*" and the conclusion that "*[t]here were significant allele frequency differences between sprint athletes and controls for both males ...and females.... Sprint athletes had a lower frequency of the XX (a-actinin-3 null) genotype...*"

The Office Action has provided no reason to doubt the accuracy or truth of the data and statements presented in the present application regarding the association between each of the recited genotypes and sprint, strength, or power performance in human males and human females. Accordingly, as set forth in MPEP §2164.04, the data provided in the present application must be relied upon for enabling support.

(iv) *Wands* Factors; Unpredictability of the Art

The Office Action opines that the presently claimed invention is not enabled in part by an analysis of the *Wands* factors (*in re Wands* 8 USPQ2d 1400 (CAFC 1988)).

The majority of the Office Action's assertions regarding each of these *Wands* factors have been rendered moot by the amendments to the claims presented herein. For example, the Office Action's explicit and implied assertions regarding excessive scope of the claims, insufficiency in the amount of direction or guidance provided and/or the presence of working examples, the unpredictability of the art, and the need for undue experimentation, are rendered moot by the

amendments to the claims presented herein. In so far as any of the Office Action's assertions are still relevant, Applicant respectfully disagrees with those assertions.

Applicant avers that methods of predicting athletic performance based on variations in the genotype of the 577 locus of the ACTN3 gene are not unpredictable.

The Office Action cites Pitsiladis *et al.* to support his proposition that genotyping to determine athletic performance is unpredictable. As quoted in the Office Action, Pitsiladis *et al.* states "although ACTN3 is an interesting candidate gene for physical performance, the use of a genetic test for this one gene cannot be justified given the multifactorial nature of sporting performance" and states "the current genetic evidence does not warrant genotyping an individual to establish their ability to run faster when this trait can be measure more effectively with a stopwatch."

The Office Action further states that Moran *et al.*, which involves a study of adolescent Greeks, found a correlation of the 577R allele with sprint performance in males but found no correlation in females, and found no correlation between the 577R allele and power performance in either males or females. The Office Action suggests that, because of this alleged unpredictability, the Applicant's claims are not enabled.

There are several flaws in this use of Pitsiladis *et al.* and Moran *et al.* to argue that the art is unpredictable.

Firstly, the Office Action has mis-characterized Pitsiladis *et al.* Pitsiladis *et al.* do not suggest that methods of predicting athletic performance based on analysis of the ACTN3 577 genotype do not work/are not enabled. Instead Pitsiladis *et al.* teach that, genetic tests for ACTN3 genotype are <u>not warranted</u> because there are multiple other variables involved in determining athletic ability, and because "one can measure athletic ability more effectively with a stopwatch." This is completely different from saying that methods of predicting athletic performance based on analysis of the ACTN3 577 genotype do not work. The fact that others may decide that they do not wish to use the methods of the present invention is irrelevant to a determination of whether the present invention is enabled.

Secondly, the Office Action seems to be equating genotype with phenotype, and assuming that if an individual has a defined genotype, such as the 577RR genotype, that individual <u>must</u> be

a good athlete, regardless of age, sex, training, nutrition or any number of other variables. This is clearly not the case.

The claimed methods provide a method of predicting potential athletic performance. Clearly variables other an individual's genotype at the ACTN3 577 locus are involved in determining an individual's actual athletic capabilities. The Applicant acknowledges this in the specification. For example, on page 28 of the application as filed, Applicant states "[o]ther methods that may be combined with the methods disclosed are based upon performance data and phenotypic predictors (e.g. height and build) and the like. ...the methods of the invention may be used to select, or at least assist in the selection of, young individuals with elite athlete potential."

The fact that Moran *et al.*, found no association between the 577R allele and athletic performance in Greek adolescent females does not mean that the presence of the 577R allele is not a predictor of potential athletic performance. For example, it is possible that the adolescent females in Moran *et al.* had not developed enhanced athletic ability, in spite of having, for example, the 577RR genotype, because they were not yet physically mature or had no prior training etc. and thus had not yet developed the phenotype of enhanced athletic ability. That does not mean that the presence of the 577R allele in those individuals might not be predictive of future potential athletic performance when other variables required for the phenotype of actual improved athletic performance were in place.

It is a basic biological principle that genotype does not equal phenotype. Hence, the vast majority of genetic tests provide only a prediction that a certain phenotype may be found in the future, and not a guarantee that that phenotype must exist, either at the time of testing or in the future. Extrapolating from the arguments in the Office Action, one could say that studies showing that children with the breast cancer susceptibility gene BRCA1 gene do not have breast cancer at the time of testing, mean that BRCAI genetic testing can not provide a predictor of a child's risk of developing breast cancer in the future. Clearly this is not true. Testing for the BRCA1 gene provides an accepted method of predicting an individual's likelihood of developing breast cancer in the future.

Thus, even if the post-filing publications of Moran *et al* or Pitsiladis *et al* suggest that there is not always a correlation between ACTN3 577 genotype and athletic performance, *which*

they do not, this is irrelevant to the question of whether the claimed methods of predicting potential athletic performance are enabled.

Furthermore, the art, when considered as a whole, is not unpredictable.

The Office Action appears to be cherry-picking which references should be considered when looking at the predictability of the correlation between ACTN3 577 genotype and athletic performance. The Office Action focuses on Moran *et al.* and Pitsiladis *et al.* (the latter of which should be completely disregarded, as discussed above) in asserting that the art is unpredictable, but has not considered the data in the present application, as well as the data in Niemi *et al.*, Papadimitrou *et al.*, and Roth *et al.*, each of which support an association between the genotypes recited in the claims and the claimed phenotypes of athletic performance, as described on pages 16-17 of the amendment filed on November 8, 2007.

Neimi *et al.*, shows, amongst other things, that the frequency of the 577RR genotype is higher in Finnish sprint athletes as compared to endurance athletes and that the frequency of the 577XX is lower in Finnish sprint athletes as compared to endurance athletes (see page 967, first full paragraph). Papadimitriou *et al*, shows that there is a higher frequency of the R allele and the 577RR genotype in Greek sprinters than in controls, and a lower frequency of the 577XX genotype (see Results section, second paragraph). Roth *et al.*, shows that the frequency of the 577XX genotype is lower in elite strength athletes than in controls (see Results and Conclusion section of one-page abstract). (Applicant notes that the Examiner was unable to read the highlighted paragraph of Papadimitriou *et al.* because this section appeared "blacked-out" after reproduction. Applicant submits herewith, in Appendix A, a copy of Papadimitriou *et al.* in the previously "blacked-out" section can be seen).

Additionally, Applicant hereby submits two additional post-filing references for the Examiner's consideration. These references are cited in the Information Disclosure Statement being filed concurrently with this amendment. The first of these references is Druzhevskaya *et al.* (*Eur. J. Appl. Physiol.* (2008), 103: 631-634). Druzhevskaya *et al.* analysed a large female cohort for power, sprint, and strength performance and showed that the frequency of the 577XX genotype and the 577X allele were significantly lower in power-oriented athletes compared to controls (see page 631, abstract). Furthermore, Druzhevskaya *et al.* found that the same finding was true in males. In the conclusions, they stated that "ACTN3 577RR and 577RX genotypes are associated with predisposition to power sports" (see Discussion, second paragraph).

The second reference is Delmonico *et al.* (*J. Gerontology*, (2007), 62A: 206-212). This reference shows a positive correlation between the number of 577R alleles in an individual and power performance after strength training in males and females (see Figure 2 and description of Figure 2 on page 209, first column, second full paragraph).

In summary, and as described above, Applicant avers that the presently claimed invention is enabled by the specification of the present application.

In view of the above remarks, and the amendments to the claims presented herein, it is respectfully requested that the rejection of claims 1-18 and 24-40 under 35 U.S.C. §112, first paragraph for lack of enablement, be reconsidered and withdrawn.

II. Claim Rejections Under 35 U.S.C. §112, 1st Paragraph, Written Description

Claims 1-16, 18, and 24-38 are rejected under 35 U.S.C. §112, first paragraph for lack of written description. Applicant respectfully disagrees with this rejection.

The Office Action opines that the specification lacks written description for any variation in any ACTN3 gene in any mammalian species.

The claims as amended herein are directed to variations in the 577 locus of the human ACTN3 gene. Accordingly, this rejection is rendered moot.

In view of the above remarks, and the amendments to the claims presented herein, it is respectfully requested that the rejection of claims 1-16, 18, and 24-38 under 35 U.S.C. §112, first paragraph, for lack of written description, be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant believes that all of the Examiner's concerns have been addressed. Accordingly, Applicant respectfully requests reconsideration and allowance of the pending claims.

A reply to this Office Action was originally due on May 13, 2008. This response is accompanied by a request for a three-month extension of time and the required fee, making the due date for response August 13, 2008. Therefore this response is being timely filed. The Commissioner is hereby authorized to charge the required fee for a small entity, as set forth in the request for extension of time, and any unforeseen fees that may be due, or to credit any over paid fees, to Deposit Account No. 08-0219.

It is requested that the undersigned be contacted at the telephone number below if it will facilitate prosecution of this application.

Respectfully submitted,

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